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ARMY ENVIRONMENTAL HYGIENE AGENCY ABERDEEN PROVING GR--ETC F/G 6/20
TOPICAL HAZARD EVALUATION PROGRAM OF CANDIDATE INSECT REPELLENT--ETC(U)
JUL 80 A W SINGER
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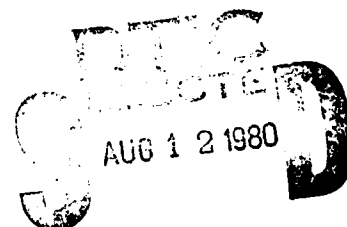
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**UNITED STATES ARMY
ENVIRONMENTAL HYGIENE
AGENCY**

ABERDEEN PROVING GROUND, MD 21010

TOPICAL HAZARD EVALUATION PROGRAM
OF CANDIDATE INSECT REPELLENTS AI3-37221 and AI3-37225
1-(3-CYCLOHEXEN-1-YLCARBONYL)-3-METHYLPYPERIDINE AND
1-(3-CYCLOHEXEN-1-YLCARBONYL)-4-METHYLPYPERAZINE
STUDY NOS. 75-51-0028-80 and 75-51-0032-80
MAY 1977 to MAY 1980



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DEPARTMENT OF THE ARMY CPT Singer/ldr/AUTOVON
U. S. ARMY ENVIRONMENTAL HYGIENE AGENCY 584-3980
ABERDEEN PROVING GROUND, MARYLAND 21010

18 JUL 1980

HSE-LT/WP

SUBJECT: Topical Hazard Evaluation Program of Candidate Insect Repellents
AI3-37221 and AI3-37225, 1-(3-cyclohexen-1-ylcarbonyl)-3-
methylpiperidine and 1-(3-cyclohexen-1-ylcarbonyl)-4-
methylpiperazine, Study Nos. 75-51-0028-80 and 75-51-0032-80,
May 1977 to May 1980

Executive Secretary
Armed Forces Pest Management Board
Forest Glen Section, WRAMC
Washington, DC 20012

A summary of the pertinent findings and recommendations of the inclosed
report follows:

Preliminary hazard evaluations of AI3-37221 and AI3-37225 were performed by
means of laboratory animal studies using rabbits and guinea pigs. Both
technical grade compounds caused moderate corneal and conjunctival
irritations. AI3-37221 caused mild primary skin irritation; AI3-37225 caused
no such reaction. AI3-37225 was tested for skin sensitization and found to
be negative. Based upon the ocular injuries, it was recommended that both
compounds be disapproved for further testing as candidate insect repellents.

FOR THE COMMANDER:

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DEPARTMENT OF THE ARMY
U. S. ARMY ENVIRONMENTAL HYGIENE AGENCY
ABERDEEN PROVING GROUND, MARYLAND 21010

HSE-LT/WP

TOPICAL HAZARD EVALUATION PROGRAM
OF CANDIDATE INSECT REPELLENTS AI3-37221 and AI3-37225
1-(3-CYCLOHEXEN-1-YLCARBONYL)-3-METHYLPYPERIDINE AND
1-(3-CYCLOHEXEN-1-YLCARBONYL)-4-METHYLPYPERAZINE
STUDY NOS. 75-51-0028-80 and 75-51-0032-80
MAY 1977 TO MAY 1980

1. AUTHORITY.

a. Letter, US Department of Agriculture-Agricultural Research Service, Southern Region, Insects Affecting Man Research Laboratory, Gainesville, Florida, 4 May 1977.

b. Memorandum of Understanding between the US Army Environmental Hygiene Agency; the US Army Health Services Command; the Department of the Army, Office of The Surgeon General; the Armed Forces Pest Control Board; and the US Department of Agriculture, Agricultural Research, Science and Education Administration; titled, Coordination of Biological and Toxicological Testing of Pesticides, effective 23 January 1979.

2. REFERENCE. Toxicology Division Procedural Guide, US Army Environmental Hygiene Agency (USAEHA), 1972, revised 1976.

3. PURPOSE. The purpose of this program is to provide guidance for further entomological testing of the candidate insect repellents AI3-37221 and AI3-37225.

4. SUMMARY OF FINDINGS. Hazard evaluations of the candidate repellents AI3-37221 and AI3-37225 were conducted by this Agency using New Zealand White rabbits for skin and eye studies and Hartley guinea pigs for a skin sensitization study. A tabular presentation of animal toxicity data developed in this Agency follows:*†

* In conducting the studies described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals," US Department of Health, Education, and Welfare Publication No. (NIH) 74-23, revised 1978.

† The experiments reported herein were performed in animal facilities fully accredited by the American Association for the Accreditation of Laboratory Animal Care.

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Study Nos. 75-51-0028-80 and 75-51-0032-80, May 77 to May 80

TABLE. PRESENTATION OF DATA

| Test | Results | Interpretation |
|--|--|------------------------------------|
| <u>SKIN IRRITATION STUDIES</u> | | |
| <u>Rabbits</u> | | |
| Single 24-hour application to intact and abraded skin of New Zealand White rabbits. | Compound AI3-37225 did not cause any irritation of the intact skin or of the skin surrounding an abrasion. | USAEHA Category I (ref Appendix). |
| 0.5 ml of each technical grade compound applied to each of six rabbits. | Compound AI3-37221 caused mild irritation of both the intact and abraded skin. | USAEHA Category II (ref Appendix). |
| <u>EYE IRRITATION STUDIES</u> | | |
| <u>Rabbits</u> | | |
| Single 24-hour application of 0.1 ml of each technical grade compound to one eye of each of six New Zealand White rabbits. | Both compounds caused moderate corneal and conjunctival injuries. This injury was still present in all eyes at 72 hrs. Evidence of corneal injury was detectable at 7 days in two rabbits for each compound. | USAEHA Category E (ref Appendix). |

Study Nos. 75-51-0028-80 and 75-51-0032-80, May 77 to May 80

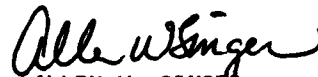
| Test | Results | Interpretation |
|---|--|---|
| <u>SENSITIZATION STUDIES</u> | | |
| <u>Guinea Pigs (Male)</u> | | |
| Intradermal injections of 0.1 ml of a 0.1 percent solution (w/v) of AI3-37225 or of dinitrochlorobenzene (DNCB)* in a mixture containing 1 volume of propylene glycol and 29 volumes of saline. | | |
| Ten test guinea pigs were given 10 sensitizing doses of AI3-37225 over a 3-week period. After 2 weeks rest, they were challenged with ID injections of test compounds. | Challenge dose of AI3-37225 did not produce a sensitization reaction. | Compound AI3-37225 did not produce a sensitization reaction under test conditions and is not expected to produce a sensitization reaction in man. |
| Ten positive control guinea pigs were sensitized over 3 weeks with DNCB. After 2 weeks rest, they were challenged with ID injections of DNCB. | Challenge dose of DNCB in positive control guinea pigs produced a marked sensitization reaction in 10 out of 10 guinea pigs. | DNCB produced a marked reaction, indicating the guinea pigs respond to sensitizing agents. |

* A known skin sensitizer

Study Nos. 75-51-0028-80 and 75-51-0032-80, May 77 to May 80

5. CONCLUSION. Both technical grade compounds caused moderate corneal injuries lasting longer than 72 hours in all rabbits, and longer than 7 days in two of six rabbits. These compounds do not qualify as nonhazardous repellents.

6. RECOMMENDATION. Under the provisions of the Memorandum of Understanding (paragraph 1b), it is recommended that AI3-37221 and AI3-37225 not be approved for further testing as candidate insect repellents.



ALLEN W. SINGER

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Laboratory Animal Veterinary Officer
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APPROVED:



ARTHUR H. MCCREESH, Ph.D.
Chief, Toxicology Division

APPENDIX

TOPICAL HAZARD EVALUATION PROGRAM
DEFINITIONS OF CATEGORIES OF COMPOUNDS BEING
CONSIDERED FOR ACUTE SKIN APPLICATION

CATEGORY I - Compounds producing no primary irritation of the intact skin or no greater than mild primary irritation of the skin surrounding an abrasion. (INTERPRETATION: No restriction for acute application to the human skin.)

CATEGORY II - Compounds producing mild primary irritation of the intact skin and the skin surrounding an abrasion. (INTERPRETATION: Should be used only on human skin found by examination to have no abrasions or may be used as a clothing impregnant.)

CATEGORY III - Compounds producing moderate primary irritation of the intact skin and the skin surrounding an abrasion. (INTERPRETATION: Should not be used directly on the skin without a prophetic patch test having been conducted on humans to determine irritation potential to human skin. May be used without patch testing, with extreme caution, as clothing impregnants. Compound should be resubmitted in the form and at the intended use concentration so that its irritation potential can be reexamined using other test techniques on animals.)

CATEGORY IV - Compounds producing moderate to severe primary irritation of the intact skin and of the skin surrounding an abrasion and, in addition, producing necrosis, vesiculation, and/or eschars. (INTERPRETATION: Should be resubmitted for testing in the form and at the intended use concentration. Upon resubmission, its irritation potential will be reexamined using other test techniques on animals, prior to possible prophetic patch testing in humans, at concentrations which have been shown not to produce primary irritation in animals.)

CATEGORY V - Compounds impossible to classify because of staining of the skin or other masking effects owing to physical properties of the compound. (INTERPRETATION: Not suitable for use on humans.)

EYE CATEGORIES:

A. Compounds noninjurious to the eye. INTERPRETATION: Irritation of human eyes is not expected if the compound should accidentally get into the eyes, provided it is washed out as soon as possible.

B. Compounds producing mild injury to the cornea. INTERPRETATION: Should be used with caution around the eyes.

C. Compounds producing mild injury to the cornea, and in addition some injury to the conjunctiva. INTERPRETATION: Should be used with caution around the eyes and mucosa.

D. Compounds producing moderate injury to the cornea. INTERPRETATION: Should be used with extreme caution around the eyes.

E. Compounds producing moderate injury to the cornea, and in addition producing some injury to the conjunctiva. INTERPRETATION: Should be used with extreme caution around the eyes and mucosa.

F. Compounds producing severe injury to the cornea and to the conjunctiva. INTERPRETATION: Should be used with extreme caution. It is recommended that use be restricted to areas other than the face.